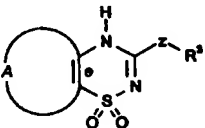


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 513/04, A61K 31/54 // (C07D 513/04, 285:00, 221:00)</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/32495 (43) International Publication Date: 1 July 1999 (01.07.99)</p>
<p>(21) International Application Number: PCT/DK98/00559 (22) International Filing Date: 17 December 1998 (17.12.98) (30) Priority Data: 1487/97 19 December 1997 (19.12.97) DK (71) Applicant (for all designated States except US): NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): DE TULLIO, Pascal [BE/BE]; 31, rue sur les Moulins, B-4020 Liège (BE). BOVERIE, Stéphane [BE/BE]; 18, avenue de la Gare, B-4460 Grâce-Hollogne (BE). SOMERS, Fabian [BE/BE]; 109, rue Lairesse, B-4020 Liège (BE). LEBRUN, Philippe [BE/BE]; 102, rue des Chats, B-1080 Bruxelles (BE). PIROTTE, Bernard [BE/BE]; 5, rue Tollet, B-4680 Oupeye (BE). NIELSEN, Flemming, Elmelund [DK/DK]; Furesø Parkvej 46, DK-2830 Virum (DK). HANSEN, John, Bondo [DK/DK]; Langaasen 3, DK-4450 Jyderup (DK). (74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: PYRIDO 1,2,4-THIADIAZINE DERIVATIVES, THEIR PREPARATION AND USE</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>Pyrido 1,2,4-thiadiazine derivatives of general formula (I) wherein Z, A and R³ are defined in the description, compositions thereof and methods for preparing the compounds are described. The compounds are useful in the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Pyrido 1,2,4-Thiadiazine Derivatives, their Preparation and UseFIELD OF THE INVENTION

- 5 The present invention relates to pyrido 1,2,4-thiadiazine derivatives, to methods for their preparation, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy e.g. in the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

10

BACKGROUND OF THE INVENTION

- Potassium channels play an important role in the physiological and pharmacological control of cellular membrane potential. Amongst the different types of potassium channels are the
- 15 ATP-sensitive (K_{ATP} -) channels which are regulated by changes in the intracellular concentration of adenosine triphosphate. The K_{ATP} -channels have been found in cells from various tissues such as cardiac cells, pancreatic cells, skeletal muscles, smooth muscles, central neurons and adenohypophysis cells. The channels have been associated with diverse cellular functions for example hormone secretion (insulin from pancreatic beta-cells, growth
- 20 hormone and prolactin from adenohypophysis cells), vasodilation (in smooth muscle cells), cardiac action potential duration, neurotransmitter release in the central nervous system.

- Modulators of the K_{ATP} -channels have been found to be of importance for the treatment of various diseases. Certain sulphonylureas which have been used for the treatment of non-
- 25 insulin-dependent diabetes mellitus act by stimulating insulin release through an inhibition of the K_{ATP} -channels on pancreatic beta-cells.

- The potassium channel openers, which comprise a heterogeneous group of compounds, have been found to be able to relax vascular smooth muscles and have therefore been used
- 30 for the treatment of hypertension.

In addition, potassium channel openers can be used as bronchodilators in the treatment of asthma and various other diseases.

Furthermore, potassium channel openers have been shown to promote hairgrowth, and have been used for the treatment of baldness.

Potassium channel openers are also able to relax urinary bladder smooth muscle and therefore, can be used for the treatment of urinary incontinence. Potassium channel openers which relax smooth muscle of the uterus can be used for treatment of premature labor. By acting on potassium channels of the central nervous system these compounds can be used for treatment of various neurological and psychiatric diseases such as Alzheimer, epilepsy and cerebral ischemia.

10

Further, the compounds are found to be useful in the treatment of benign prostatic hyperplasia, erectile dysfunction and in contraception.

Compounds of the present invention, which inhibit insulin secretion by activating potassium channels of the beta-cell can be used in combination with other compounds which may be used to treat non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus. Examples of such compounds are insulin, insulin sensitizers, such as thiazolidinediones, insulin secretagogues, such as repaglinide, tolbutamide, glibenclamide and glucagon like peptide (GLP1), inhibitors of α -glucosidases and hepatic enzymes responsible for the biosynthesis of glucose.

20

Recently, it has been shown that Diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide) and certain 3-(alkylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide derivatives inhibit insulin release by an activation of K_{ATP} -channels on pancreatic beta-cells (Pirotte B. et al. *Biochem. Pharmacol.* 47, 1381-1386 (1994); Pirotte B. et al., *J. Med. Chem.*, 36, 3211-3213 (1993). Diazoxide has furthermore been shown to delay the onset of diabetes in BB-rats (Vlahos WD et al. *Metabolism* 40, 39-46 (1991)). In obese Zucker rats diazoxide has been shown to decrease insulin secretion and increase insulin receptor binding and consequently improve glucose tolerance and decrease weight gain (Alemzadeh R. et al. *Endocrinol.* 133, 705-712, 1993). It is expected that compounds which activate K_{ATP} -channels can be used for treatment of diseases characterised by an overproduction of insulin and for the treatment and prevention of diabetes.

30

EP 618 209 discloses a class of pyridothiadiazine derivatives having an alkyl or an alkylamino group in position 3 of the thiadiazine ring. These compounds are claimed to be agonists at the AMPA-glutamate receptor.

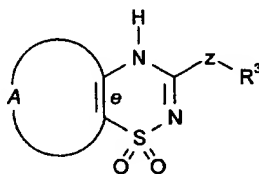
- 5 In J. Med. Chem. 1980, 23, 575-577 the synthesis of 4(5)-amino-and formylaminoimidazo-5(4) carboxamide and their properties as agents of chemotherapeutic value are described. Especially, the compounds 3-aminoimidazo[4,5-e]-1,2,4-thiadiazine 1,1-dioxide and N-benzoylaminoimidazo[4,5-e]-1,2,4-thiadiazine 1,1-dioxide are shown.

10

DESCRIPTION OF THE INVENTION

The present invention relates to pyrido 1,2,4-thiadiazine derivatives of the general formula I:

15



(I)

wherein Z is O, S, S(=O), S(=O)₂, S(=NR), S(=O)(=NR) or S(=NR)₂

20

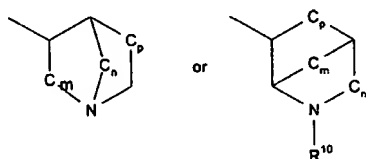
wherein R is hydrogen; C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen, hydroxy or C₁₋₆-alkoxy; or C₃₋₆-cycloalkyl optionally mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy;

- 25 R³ is C₃₋₆-cycloalkyl or (C₃₋₆-cycloalkyl)C₁₋₆-alkyl the C₃₋₆-cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C₁₋₆-monoalkyl or dialkylamino; or
- 30 straight or branched C₁₋₁₈-alkyl, C₂₋₁₈-alkenyl or C₂₋₁₈-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₃₋₆-

cycloalkyl, nitro, amino, C₁₋₆- monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C₁₋₆-alkoxycarbonyl, carbamoyl, formylamino, or C₁₋₆-alkylcarbonylamino, aryl, aryloxy, arylalkoxy, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, acyl or C₁₋₆-alkoxycarbonyl;

or R³ is

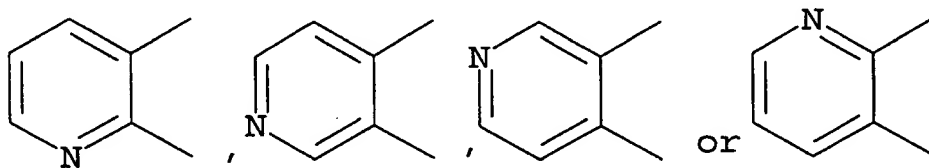
10



wherein n,m,p independently are 0,1,2,3 and R¹⁰ is hydrogen; hydroxy; C₁₋₆-alkoxy; C₃₋₆-cycloalkyl optionally mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen;

15

A together with the carbon atoms forming bond e of formula I forms a pyridine ring selected from



20

the pyridine ring optionally being mono- or polysubstituted with halogen; C₁₋₁₈-alkyl; C₃₋₆-cycloalkyl; hydroxy; C₁₋₆-alkoxy; C₁₋₆-alkoxy-C₁₋₆-alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C₁₋₆-monoalkyl- or dialkylamino; sulfamoyl; C₁₋₆-alkylthio; C₁₋₆-alkylsulfonyl; C₁₋₆-alkylsulfinyl; C₁₋₆-alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy; C₁₋₆-alkoxycarbonyl; C₁₋₆-alkoxycarbonyl-C₁₋₆-alkyl; carbamyl; carbamylmethyl; C₁₋₆-monoalkyl- or dialkylaminocarbonyl; C₁₋₆-monoalkyl- or dialkylaminothi-

25

ocarbonyl; ureido; C₁₋₆-monoalkyl- or dialkylaminocarbonylamino, thiocarbamyl; thioureido; C₁₋₆-monoalkyl- or dialkylaminothiocarbonyl- amino; C₁₋₆-monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy-C₁₋₆-alkyl; acyl; formyl; or a 5 - 6 membered nitrogen, oxygen or sulfur containing ring, optionally substituted with C₁₋₆-alkyl or phenyl, the phenyl group optionally being
5 mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy;

or a salt thereof with a pharmaceutically acceptable acid or base.

Within its scope the invention includes all optical isomers of compounds of formula I, some
10 of which are optically active, and also their mixtures including racemic mixture thereof.

The scope of the invention also includes all tautomeric forms of the compounds of formula I.

The salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable
15 ble metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethane sulfonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by
20 reference, or lithium, sodium, potassium, magnesium and the like.

The term "C₁₋₆-alkoxy" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C₁₋₆-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 6 carbon atoms e.g.
25 methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

The term "C₁₋₆-alkylthio" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a lower alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 6 carbon atoms e.g.
30 methylthio, ethylthio, propylthio, butylthio, pentylthio.

The terms "C₂₋₆-alkenyl", "C₂₋₁₈-alkenyl" and "C₈₋₁₈-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having 2-6, 2-18 or 8-18 carbon atoms, respectively, and

one double bond such as e.g. vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl.

The term "C₃₋₆-cycloalkyl" as used herein refers to a radical of a saturated cyclic hydrocarbon with the indicated number of carbons such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The terms "C₂₋₆-alkynyl", "C₂₋₁₈-alkynyl" and "C₈₋₁₈-alkynyl" as used herein refers to unsaturated hydrocarbons which contain triple bonds, such as e.g. -C≡CH, -C≡CCH₃, -CH₂C≡CH, -CH₂CH₂C≡CH, -CH(CH₃)C≡CH, and the like.

The term "C₁₋₆-alkoxy-C₁₋₆-alkyl" as used herein refers to a group of 2-12 carbon atoms interrupted by an O such as e.g. CH₂-O-CH₃, CH₂-O-CH₂-CH₃, CH₂-O-CH(CH₃)₂ and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The terms "C₁₋₆-alkyl", "C₁₋₁₂-alkyl" and "C₁₋₁₈-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms such as e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylpentyl, neopentyl, n-hexyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like. The term "C₁₋₁₈-alkyl" as used herein also includes secondary C₃₋₆-alkyl and tertiary C₄₋₆-alkyl.

The term "C₁₋₆-monoalkylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms such as e.g. methylamino, ethylamino, propylamino, n-butylamino, sec-butylamino, isobutylamino, tert-butylamino, n-pentylamino, 2-methylbutylamino, n-hexylamino, 4-methylpentylamino, neopentylamino, n-hexylamino, 2,2-dimethylpropylamino and the like.

The term "C₁₋₆-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

The term "C₁₋₆-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "3-6 membered saturated ring system" as used herein refers to a monovalent substituent comprising a monocyclic saturated system containing one or more hetero atoms selected from nitrogen, oxygen and sulfur and having 3-6 members and having its free valence from a carbon atom, e.g. 2-pyrrolidyl, 4-piperidyl, 3-morpholinyl, 1,4-dioxan-2-yl, 5-oxazolidinyl, 4-isoxazolidinyl, or 2-thiomorpholinyl.

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl, and 9-bicyclo[3.3.1]nonanyl.

The term "aryl" as used herein refers to phenyl, 1-naphthyl, or 2-naphthyl.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine, and purine.

The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

5

The term "aryloxy" as used herein refers to phenoxy, 1-naphthoxy or 2-naphthoxy.

The term "arylalkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphthyl)ethoxy and the like.

10

The term "C₁₋₆-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.

15

The term "C₁₋₆-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a sulfonyl group such as e.g. methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.

25

The term "C₁₋₆-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a sulfonyl group such as dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

30

The term "C₁₋₆-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C₁₋₆-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

The term "C₁₋₆-alkylcarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

- 5 The term "(C₃₋₆-cycloalkyl)C₁₋₆-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C₃₋₆-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the
10 like.

- The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; e.g.
15 phenylthio, (4-methylphenyl)-thio, (2-chlorophenyl)thio, and the like.

- The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-S(=O)-), the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.
20

- The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.

- 25 The term "C₁₋₆-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylamino-carbonyl, n-
30 hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.

The term "C₁₋₆-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a carbonyl group such as dimethylaminocarbo-

nyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.

The term "C₁₋₆-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C₁₋₆-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylaminocarbonylamino, n-propylaminocarbonylamino, isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino, isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

10

The term "C₁₋₆-dialkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C₁₋₆-dialkylaminocarbonyl group, such as dimethylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbonylamino, dipropylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.

15

The term "5- or 6-membered nitrogen, oxygen or sulfur containing ring" as used herein refers to a monovalent substituent comprising a monocyclic unsaturated or saturated system containing one or more nitrogen, oxygen or sulfur atoms and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholino, thiomorpholino, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, and 1,4-dioxolanyl.

25 Preferred compounds of the invention are:

3-cyclopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclobutylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopentylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
30 3-cyclopropylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclohexylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclohexylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-(1-phenylethyl)sulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

- 3-ethylsulfinimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfonimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfinimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfinyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
5 3-cyclopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclobutoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopentoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
10 6-chloro-3-cyclobutylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopentylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclohexylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclohexylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
15 6-chloro-3-(1-phenylethyl)sulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-ethylsulfinyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-ethylsulfinimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-ethylsulfonimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-isopropylsulfinimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
20 6-chloro-3-isopropylsulfinyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylmethoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclobutoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopentoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
25 3-cyclopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclobutylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopentylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclohexylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
30 3-cyclohexylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-(1-phenylethyl)sulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfinimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfonimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

- 3-isopropylsulfinimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
5 3-cyclobutoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopentoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopentylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
10 7-chloro-3-cyclohexylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclohexylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-(1-phenylethyl)sulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-ethylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-ethylsulfinimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
15 7-chloro-3-ethylsulfonimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-isopropylsulfinimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-isopropylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopropoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopropylmethoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
20 7-chloro-3-cyclobutoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopentoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-propylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
25 3-cyclopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-(1,2-dimethylpropyl)sulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isobutylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-propoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
30 3-isopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-(1,2-dimethylpropoxy)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isobutoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

- 3-ethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-ethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
5 3-isopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-isopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
10 7-chloro-3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

The compounds of the present invention interact with the potassium channels and hence act
15 as openers or blockers of the ATP-regulated potassium channels, which make them useful in
the treatment of various diseases of the cardiovascular system, e.g. cerebral ischemia, hy-
pertension, ischemic heart diseases, angina pectoris and coronary heart diseases; the pul-
monary system; the gastrointestinal system; the central nervous system and the endocrino-
logical system.

20

Since some K_{ATP} -openers are able to antagonize vasospasms in basilar or cerebral arteries
the compounds of the present invention can be used for the treatment of vasospastic disor-
ders such as subarachnoid haemorrhage and migraine.

25 The compounds of the present invention may also be used for the treatment of diseases as-
sociated with decreased skeletal muscle blood flow such as Raynauds disease and inter-
mittent claudication.

Further, the compounds of the invention may be used for the treatment of chronic airway
30 diseases, including asthma, and for treatment of detrusor muscle instability secondary to
bladder outflow obstruction and therefore for kidney stones by aiding their passage along the
urethra.

The present compounds could also be used for treatment of conditions associated with disturbances in gastrointestinal mobility such as irritable bowel syndrome. Additionally these compounds can be used for the treatment of premature labour and dysmenorrhea.

- 5 Potassium channel openers hyperpolarize neurons and inhibit neurotransmitter release and it is expected that such compounds can be used for the treatment of various diseases of the central nervous system, e.g. epilepsy, ischemia and neurodegenerative diseases, and for the management of pain.
- 10 Further, potassium channel openers promote hairgrowth, therefore, the compounds of the present invention can be used for the treatment of baldness.

Potassium channel openers also relax urinary bladder smooth muscle, thus, the compounds of the present invention can be used for the treatment of urinary incontinence.

15

- In diseases such as nesidioblastosis and insulinoma in which a hypersecretion of insulin causes severe hypoglycemia the compounds of the present invention can be used to reduce insulin secretion. In obesity hyperinsulinemia and insulin resistance is very frequently encountered. This condition could lead to the development of noninsulin dependent diabetes (NIDDM). It is expected that potassium channel openers, and hence the compounds of the
- 20 present invention, can be used for reducing the hyperinsulinemia and thereby prevent diabetes and reduce obesity. In overt NIDDM treatment of hyperinsulinemia with potassium channel openers, and hence the present compounds, can be of benefit in restoring glucose sensitivity and normal insulin secretions.

25

In early cases of insulin dependent diabetes (IDDM) or in prediabetic cases, potassium channel openers and hence the present compounds can be used to induce pancreatic cell rest which may prevent the progression of the autoimmune disease.

- 30 The potassium channel openers of the present invention can be administered in combination with an immunosuppressant or with an agent like nicotinamide, which will reduce autoimmune degeneration of beta-cells.

Combining beta-cell rest with a treatment protecting the beta-cells against cytokine mediated beta-cell impairment/cytotoxicity is another aspect of this invention.

Insulin requiring or Type 1 diabetes (IDDM) as well as late onset IDDM (also known as type 1.5. e.g. non-insulin-requiring Type 2 (NIDDM) patients with autoreactivity against beta-cell epitopes that later turns insulin requiring) have circulating autoreactive monocytes/lymphocytes that homes to the islets/beta-cells and releases their cytokines. Some of these cytokines (e.g. interleukin-1b (IL-1b) , tumour necrosis factor a (TNFa) and interferon g (IFNg)) are specifically toxic to the beta-cells, e.g. through the induction of nitric oxide (NO) and other free radicals. Inhibition of this cytotoxicity, e.g. by co-administring nicotinamide (NA), a derivative hereof or other cytokine protective compounds to the prediabetic/diabetic patients treated with the PCO compound is an example of this aspect. Nicotinamide belongs to the B-vitamin family and is derived from nicotinic acid by amidation of the carboxyl group. It processes none of nicotine's pharmacological properties. NA is converted into NAD⁺, which acts as a coenzyme for proteins involved in tissue respiration. NA has been proposed to influence several of the putative intracellular molecular events following immune attack on the beta-cells. Animal experiments and early non-blinded experiments in humans have indicated a protective role of this compound against IDDM as well as in cytokine/immune mediated beta-cell destruction.

Yet another aspect of this application concerns the use of a PCO compound alone or in combination with the inhibitor of cytokine/immune mediated beta-cell impairment , in transplantation, e.g. islet transplantation into diabetes patients. The use of one or both of these treatments may reduce the risk of rejection of the transplanted islets/beta-cells/engineered beta-cells/pancreas.

Compounds of the present invention which act as blockers of K_{ATP} -channels can be used for the treatment of NIDDM.

Preferably, the compounds of the present invention may be used for treatment or prevention of diseases of the endocrinological system such as hyperinsulinaemia and diabetes.

30

Accordingly, in another aspect the invention relates to a compound of the general formula I or a pharmaceutically acceptable acid addition salt thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of hyperinsulinaemia and treatment or prevention of diabetes.

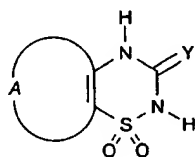
Furthermore, the invention also relates to the use of the inventive compounds of formula I as medicaments useful for treating hyperinsulinaemia and treating or preventing diabetes

- 5 Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more other pharmacologically active compounds, e.g. an antidiabetic or other pharmacologically active material, including compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathophysiological mechanism. Suitable antidiabetics comprise insulin as well as orally ac-
- 10 tive hypoglycaemic agents such as sulphonylureas, e.g. glibenclamide and glipizide; biguanides, e.g. metformin; benzoic acid derivatives, e.g. repaglinide; and thiazolidinediones, e.g. troglitazone and ciglitazone.

In yet another aspect, the present invention relates to methods of preparing the above mentioned compounds. The methods comprises:

15

a) reacting a compound of formula II:



(II)

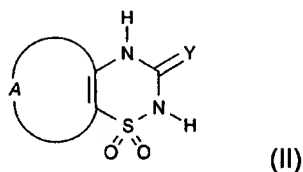
wherein Y is O or S and A is as defined above with a compound of formula III



wherein R^3 is as defined above and X is a leaving group such as halogen or sulfate, preferentially chloro, bromo or iodo to form a compound of the general formula I wherein Z is O or S. The reaction may be carried out in a suitable solvent and in the presence of a base, or

17

b) reacting a compound of formula II:



5

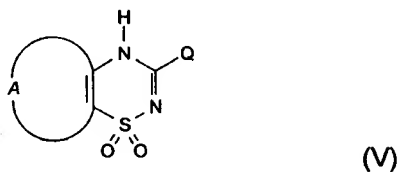
wherein Y is O and A is as defined above with a diazo compound of formula IV



10

wherein R' and R'' together as two substituents on methyl form a group R'R''CH meeting the criteria defined above for R³, to form a compound of the general formula I wherein Z is O and R³ is R'R''CH, or

15 c) reacting a compound of formula V:

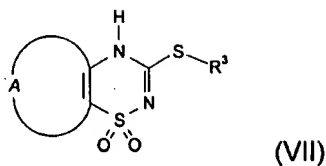


20 wherein Q is a leaving group such as halogen, preferentially chloro, bromo, iodo; amino, trimethylamino, imidazol-1-yl, methylsulfanyl, methylsulfinyl or methylsulfonyl with a compound of formula VI:



25 wherein R³ is as defined above and Y is O or S to form a compound of the general formula I wherein Z is O or S. The reaction may be carried out in a suitable solvent and in the presence of a base, or

d) reacting a compound of formula VII:

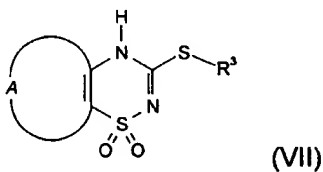


5

wherein A and R³ are as defined above with an oxidizing agent to form a compound of the general formula I wherein Z is S(=O) or S(=O)₂, or

10

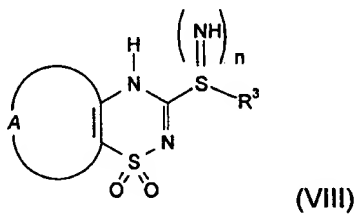
e) reacting a compound of formula VII:



15

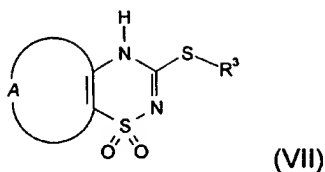
wherein A and R³ are as defined above with an aminating agent according to known procedures, see e.g. P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1980) 477-498 and P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1975) 189-209, to form a compound of the general formula VIII

20



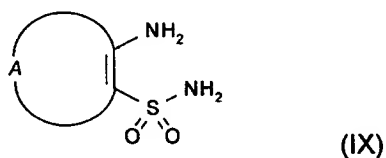
wherein n is 1 or 2, or

f) reacting a compound of formula VII:



5 wherein A and R³ are as defined above with an aminating agent and subsequently an oxidizing agent, or vice versa, according to known procedures, see e.g. P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1980) 477-498 and P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1975) 189-209, to form a compound of the general formula I wherein Z is S(=O)(=NR), or

10 g) reacting a compound of formula IX



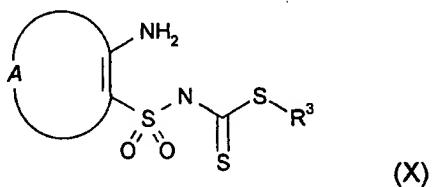
15

wherein A is as defined above with CS₂ in the presence of a base to give the corresponding sulfonylimino carbodithioate which in turn is treated with an alkylating agent of formula III

20



wherein R³ is as defined above and X is a leaving group such as halogen or sulfate, preferentially chloro, bromo or iodo to form a compound of formula X

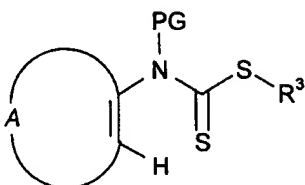


25

which by ring-closure, e.g. by treatment with phosgene in a suitable solvent, forms a compound of the general formula I, or

5

h) reacting a compound of formula XI



(XI)

- 10 wherein A and R³ are as defined above and PG is a protecting group, e.g. substituted benzyl, with chlorosulfonyl isocyanate (Cl-SO₂-NCO) and subsequent ring closure followed by removal of the protecting group to form a compound of formula I.

The starting materials are either known compounds or compounds which may be prepared in analogy with the preparation of known compounds or in analogy with known methods as described by e.g. Huang B.-S., et al., J. Med. Chem., 23, 575-7 (1980), Ofitserov V. I. et al., Khim. Geterotsikl. Soedin., 1119-22 (russ.) (1976), Topliss J. G., U.S. 3,641,017 (1972), Kotovskaya S. K. et al., Khim.-Farm. Zh., 13, 54-57 (russ.) (1979), Meyer R. F., J. Heterocycl. Chem., 6, 407-408 (1969), Hattori M., Yoneda M., Goto M., Bull. Chem. Soc. Jap., 46, 1890-1 (1973), Williams T.R. and Cram D.J., J. Org. Chem., 38, 20-26 (1973), T. Iwakawa, H. Tamura, Y. Hayase, Chem.Pharm.Bull. 38(4), 1075-6 (1990), F.E. Nielsen, H.C. Hansen, J.B. Hansen, T.M. Tagmose, PCT Int. Appl. WO 97 / 26265, M.E. Arranz, S. Vega, Heterocycles 45, 1767-1774 (1997).

25 PHARMACOLOGICAL METHODS

The ability of the compounds to interact with potassium channels can be determined by various methods. When patch-clamp techniques (Hamill O.P., Marty A., Neher E., Sakmann B. and Sigworth F.J., *Plügers Arch.*, 391, 85-100 (1981)) are used the ionic current through a single channel of a cell can be recorded.

30

The activity of the compounds as potassium channel openers can also be measured as relaxation of rat aorta rings according to the following procedure:

- 5 A section of rat thoracic aorta between the aortic arch and the diaphragm was dissected out and mounted as ring preparations as described by Taylor P.D. et al , *Brit J. Pharmacol*, 111, 42-48 (1994).

After a 45 min. equilibration period under a tension of 2 g, the preparations were contracted
10 to achieve 80% of the maximum response using the required concentration of phenylephrine. When the phenylephrine response reached a plateau, potential vasodilatory agents were added cumulatively to the bath in small volumes using half log molar increments at 2 min intervals. Relaxation was expressed at the percentage of the contracted tension. The potency of a compound was expressed as the concentration required to evoke a 50% relaxation of
15 the tissue.

In the pancreatic b-cell the opening of the K_{ATP} -channels can be determined by measuring the subsequent change in the concentration of cytoplasmic free Ca^{2+} concentration according to the method of Arkhammar P. et al. , *J. Biol. Chem.*, 262, 5448-5454 (1987).

20

$^{86}Rb^{+}$ efflux from a β -cell line

The RIN 5F cell line was grown in RPMI 1640 with Glutamax I, supplemented with 10 % fetal calf serum (from GibcoBRL, Scotland, UK) and maintained in an atmosphere of 5 % CO_2 /
25 95 % air at 37°C. The cells were detached with a Trypsin-EDTA solution (from GibcoBRL, Scotland, UK), resuspended in medium, added 1 mCi/ml $^{86}Rb^{+}$ and replated into microtiter plates (96 well cluster 3596, sterile, from Costar Corporation, MA, USA) at a density of 50000 cells/well in 100 μ l/well, and grown 24 hours before use in assay.

- 30 The plates were washed 4 times with Ringer buffer (150 mM NaCl, 10 mM Hepes, 3.0 mM KCl, 1.0 mM $CaCl_2$, 20 mM Sucrose, pH 7.1). Eighty μ l Ringer buffer and 1 μ l control- or test compound dissolved in DMSO was added. After incubation 1 h at room temperature with a lid, 50 μ l of the supernatant was transferred to PicoPlates (Packard Instrument Company, CT, USA) and 100 μ l MicroScint40 (Packard Instrument Company, CT, USA) added. The

plates were counted in TopCount (Packard Instrument Company, CT, USA) for 1 min/well at the ^{32}P program.

The calculation of EC_{50} and E_{max} was done by SlideWrite (Advanced Graphics Software, Inc., CA, USA) using a four parameter logistic curve: $y = (a-d)/(1+(x/c)^b)+d$, where a = the activity estimated at concentration zero, b = a slope factor, c = the concentration at the middle of the curve and, d = the activity estimated at infinite concentration. $\text{EC}_{50} = c$ and $\text{E}_{\text{max}} = d$, when the curve is turned of at infinite concentrations.

10 The compounds according to the invention are effective over a wide dose range. In general satisfactory results are obtained with dosages from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, per day. A most preferable dosage is about 1 mg to about 100 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulo-

se and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

10

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

15

Generally, the compounds are dispensed in unit form comprising from about 1 to about 100 mg in a pharmaceutically acceptable carrier per unit dosage.

20

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

25	Active compound	5.0 mg
	Lactosum	67.8 mg Ph.Eur.
	Avicel®	31.4 mg
	Amberlite®	1.0 mg
	Magnesii stearas	0.25 mg Ph.Eur.

30

EXAMPLES

The process of preparing the compounds of formula I is further illustrated in the following examples which, however, are not to be construed as limiting.

General procedures for the preparation of 3-alkylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxides

5 Method A

The appropriate 2,3-dihydro-3-thioxo-4H-pyrido-1,2,4-thiadiazine 1,1-dioxide (0.6 g) was dissolved in a solution of sodium hydrogen carbonate (0.44 g) in water (18 mL) and methanol (12 mL) and supplemented with an excess of the appropriate alkyl halide (1.0 - 1.5 mL). The mixture was stirred at room temperature for a few hours (until completion of the reaction checked by t.l.c.). Methanol and the excess of the reagent were removed by distillation under reduced pressure. The aqueous suspension of the crude compound was supplemented with 4N NaOH until dissolution. The alkaline solution was treated with charcoal, filtered off, and the filtrate was adjusted to pH 4-5 with formic acid. The resulting precipitate was collected by filtration, washed with water and dried (yields: 45-50 %).

Method B

The appropriate 2,3-dihydro-3-thioxo-4H-pyrido-1,2,4-thiadiazine 1,1-dioxide (0.5 g) and anhydrous potassium carbonate (0.32 g) were introduced in a mixture of acetonitrile (20 mL) and DMF (5 mL). The suspension was supplemented with an excess of the appropriate alkyl halide (1 - 1.5 mL) and then heated at 50°C for 2 h. The completion of the reaction was controlled by t.l.c. The solvents were removed by distillation under reduced pressure and the residue was dissolved in 2N NaOH (30-50 mL). The alkaline solution was treated with charcoal, filtered off, and the filtrate was adjusted to pH 2-3 with 6N HCl. The resulting precipitate was collected by filtration, washed with water and dried (yields: 45-50 %).

EXAMPLE 1

30

3-Isopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate

The title compound was obtained from 2,3-dihydro-3-thioxo-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate (B. Pirotte et al, *J. Med. Chem.* 36, 1993, 3211) and

isopropyl iodide as described in method A; mp 80-82 °C; IR (KBr): 3490, 3227, 2927, 1600, 1550, 1475, 1315, 1296, 1204, 1183, 1165, 1104 cm⁻¹.

EXAMPLE 2

5

3-Isopropylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was obtained from 2,3-dihydro-7-methyl-3-thioxo-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (C.G. Neill et al, *Tetrahedron*.54, 1998, 13645) and isopropyl iodide as described in method A. The crude compound was recrystallized from methanol; mp 226-
10 228 °C; IR (KBr): 3128, 2967, 1603, 1553, 1500, 1456, 1320, 1300, 1217, 1204, 1162, 1083 cm⁻¹.

EXAMPLE 3

15

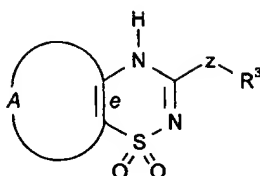
3-Cyclopropylmethylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was obtained from 2,3-dihydro-7-methyl-3-thioxo-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide and cyclopropylmethyl bromide as described in method B; mp 254-
255 °C; IR (KBr): 3128, 2936, 2794, 1604, 1554, 1498, 1456, 1317, 1301, 1216, 1203, 1157,
1082 cm⁻¹.

20

CLAIMS

1. A compound of the general formula I:



(I)

- 10 wherein Z is O, S, S(=O), S(=O)₂, S(=NR), S(=O)(=NR) or S(=NR)₂

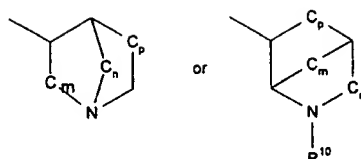
wherein R is hydrogen; C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen, hydroxy or C₁₋₆-alkoxy; or C₃₋₆-cycloalkyl optionally mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy;

15

R³ is C₃₋₆-cycloalkyl or (C₃₋₆-cycloalkyl)C₁₋₆-alkyl the C₃₋₆-cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C₁₋₆-monoalkyl or dialkylamino; or
 20 straight or branched C₁₋₁₈-alkyl, C₂₋₁₈-alkenyl or C₂₋₁₈-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkyl, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C₁₋₆-alkoxycarbonyl, carbamoyl, formylamino, or C₁₋₆-alkylcarbonylamino, aryl, aryloxy, a-
 25 rylalkoxy, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, acyl or C₁₋₆-alkoxycarbonyl;

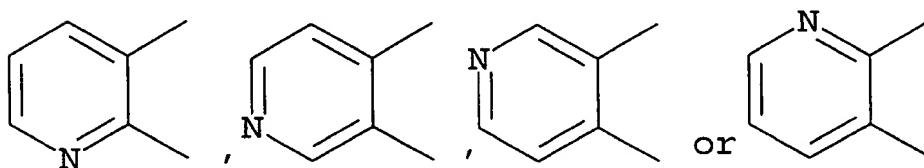
30

or R^3 is



- 5 wherein n, m, p independently are 0, 1, 2, 3 and R^{10} is hydrogen; hydroxy; C_{1-6} -alkoxy; C_{3-6} -cycloalkyl optionally mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen;

- 10 A together with the carbon atoms forming bond e of formula I forms a pyridine ring selected from

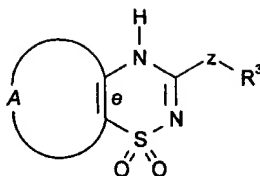


- the pyridine ring optionally being mono- or polysubstituted with halogen; C_{1-18} -alkyl; C_{3-6} -cycloalkyl; hydroxy; C_{1-6} -alkoxy; C_{1-6} -alkoxy- C_{1-6} -alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C_{1-6} -monoalkyl- or dialkylamino; sulfamoyl; C_{1-6} -alkylthio; C_{1-6} -alkylsulfonyl; C_{1-6} -alkylsulfinyl; C_{1-6} -alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C_{1-6} -alkyl, perhalomethyl, halogen, hydroxy or C_{1-6} -alkoxy; C_{1-6} -alkoxycarbonyl; C_{1-6} -alkoxycarbonyl- C_{1-6} -alkyl; carbamyl; carbamylmethyl; C_{1-6} -monoalkyl- or dialkylaminocarbonyl; C_{1-6} -monoalkyl- or dialkylaminothiocarbonyl; ureido; C_{1-6} -monoalkyl- or dialkylaminocarbonylamino, thiocarbamyl; thioureido; C_{1-6} -monoalkyl- or dialkylaminothiocarbonyl- amino; C_{1-6} -monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy- C_{1-6} -alkyl; acyl; formyl; or a 5 - 6 membered nitrogen, oxygen or sulfur containing ring, optionally substituted with C_{1-6} -alkyl or phenyl, the phenyl group optionally being
- 25 mono- or polysubstituted with C_{1-6} -alkyl, perhalomethyl, halogen, hydroxy or C_{1-6} -alkoxy;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

2. A compound of the general formula I:

5



(I)

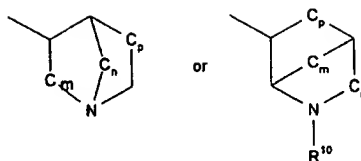
wherein Z is O, S, S(=O), S(=O)₂, S(=NR), S(=O)(=NR) or S(=NR)₂

10

wherein R is hydrogen; C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen, hydroxy or C₁₋₆-alkoxy; or C₃₋₆-cycloalkyl optionally mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy;

- 15 R³ is C₃₋₆-cycloalkyl or (C₃₋₆-cycloalkyl)C₁₋₆-alkyl the C₃₋₆-cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C₁₋₆-monoalkyl or dialkylamino; or
- 20 straight or branched C₁₋₁₈-alkyl, C₂₋₁₈-alkenyl or C₂₋₁₈-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkyl, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C₁₋₆-alkoxycarbonyl, carbamoyl, formylamino, or C₁₋₆-alkylcarbonylamino, aryl, aryloxy, arylalkoxy, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, acyl or C₁₋₆-alkoxycarbonyl;

30 or R³ is

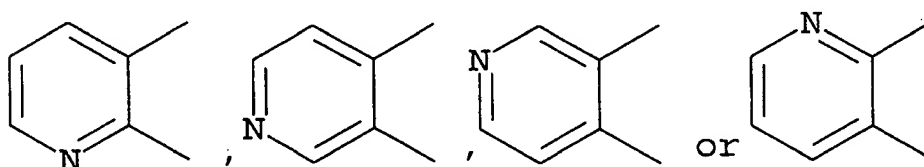


wherein n,m,p independently are 0,1,2,3 and R¹⁰ is hydrogen; hydroxy; C₁₋₆-alkoxy; C₃₋₆-

- 5 cycloalkyl optionally mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen;

A together with the carbon atoms forming bond e of formula I forms a pyridine ring selected from

10

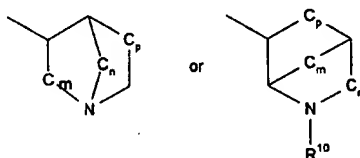


- the pyridine ring optionally being mono- or polysubstituted with halogen; C₁₋₁₈-alkyl; C₃₋₆-
cycloalkyl; hydroxy; C₁₋₆-alkoxy; C₁₋₆-alkoxy-C₁₋₆-alkyl; nitro; amino; cyano; cyanomethyl; per-
15 halomethyl; C₁₋₆-monoalkyl- or dialkylamino; sulfamoyl; C₁₋₆-alkylthio; C₁₋₆-alkylsulfonyl; C₁₋₆-
alkylsulfinyl; C₁₋₆-alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, aryl, arylalkyl, aryloxy,
the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halo-
gen, hydroxy or C₁₋₆-alkoxy; C₁₋₆-alkoxycarbonyl; C₁₋₆-alkoxycarbonyl-C₁₋₆-alkyl; carbamyl;
carbamylmethyl; C₁₋₆-monoalkyl- or dialkylaminocarbonyl; C₁₋₆-monoalkyl- or dialkylaminothi-
20 ocarbonyl; ureido; C₁₋₆-monoalkyl- or dialkylaminocarbonylamino, thiocarbamyl; thioureido;
C₁₋₆-monoalkyl- or dialkylaminothiocarbonyl- amino; C₁₋₆-monoalkyl- or dialkylaminosulfonyl;
carboxy; carboxy-C₁₋₆-alkyl; acyl; formyl; or a 5 - 6 membered nitrogen, oxygen or sulfur con-
taining ring, optionally substituted with C₁₋₆-alkyl or phenyl, the phenyl group optionally being
mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy;

25

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or
mixture of optical isomers, including a racemic mixture, or any tautomeric form

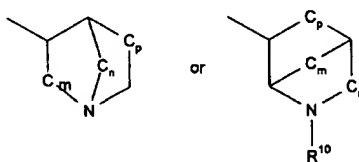
- provided that when Z is O, R³ is C₃₋₆-cycloalkyl or (C₃₋₆-cycloalkyl)C₁₋₆-alkyl the C₃₋₆-cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl,
- 5 C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C₁₋₆-monoalkyl or dialkylamino; or straight or branched C₈₋₁₈-alkyl, C₈₋₁₈-alkenyl or C₈₋₁₈-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkyl, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C₁₋₆-alkoxycarbonyl, carbamoyl, formylamino, or C₁₋₆-
- 10 alkylcarbonylamino, aryl, aryloxy, arylalkoxy, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, acyl or C₁₋₆-alkoxycarbonyl;
- 15 or R³ is



- 20 wherein n,m,p independently are 0,1,2,3 and R¹⁰ is hydrogen; hydroxy; C₁₋₆-alkoxy; C₃₋₆-cycloalkyl optionally mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen;
- and further provided that when Z is S, R³ is C₃₋₆-cycloalkyl or (C₃₋₆-cycloalkyl)C₁₋₆-alkyl the C₃₋₆-cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C₁₋₆-monoalkyl or dialkylamino; or straight or branched C₈₋₁₈-alkyl, C₂₋₁₈-alkenyl or C₂₋₁₈-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₃₋₆-cycloalkyl, nitro, amino, C₁₋₆-monoalkyl- or dialkylami-
- 25
- 30

no, cyano, oxo, formyl, acyl, carboxy, C₁₋₆-alkoxycarbonyl, carbamoyl, formylamino, or C₁₋₆-alkylcarbonylamino, aryl, aryloxy, arylalkoxy, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, perhalomethyl, halogen, hydroxy or C₁₋₆-alkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, aryloxy, arylalkoxy, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, oxo, acyl or C₁₋₆-alkoxycarbonyl;

or R³ is



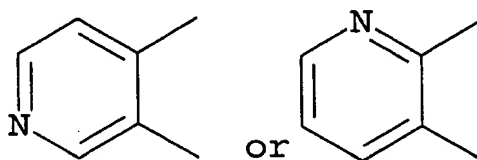
10

wherein n,m,p independently are 0,1,2,3 and R¹⁰ is hydrogen; hydroxy; C₁₋₆-alkoxy; C₃₋₆-cycloalkyl optionally mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen.

15

3. A compound according to claim 1 wherein A together with the carbon atoms forming bond e of formula I forms a pyridine ring selected from

20



the pyridine ring optionally being mono substituted with C₁₋₁₈-alkyl.

4. A compound according to claim 1 or 3 wherein Z is S.

25

5. A compound according to claim 1, 3 or 4 wherein R³ is (C₃₋₆-cycloalkyl)C₁₋₆-alkyl or branched C₁₋₁₈-alkyl.

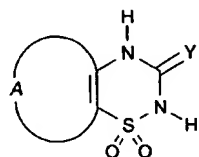
6. A compound according to claim 5 wherein R³ is isopropyl.
7. A compound according to claim 5 wherein R³ is cyclopropylmethyl.
- 5 8. A compound selected from the following:
3-isopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide.
- 10 9. A compound selected from the following:

3-cyclopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclobutylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
15 3-cyclopentylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclohexylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclohexylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-(1-phenylethyl)sulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
20 3-ethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfonimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfonimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfonimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
25 3-cyclopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclobutoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopentoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
30 6-chloro-3-cyclobutylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopentylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclohexylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclohexylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

- 6-chloro-3-(1-phenylethyl)sulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-ethylsulfinyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-ethylsulfinimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-ethylsulfonimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
5 6-chloro-3-isopropylsulfinimidoyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-isopropylsulfinyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylmethoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclobutoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
10 6-chloro-3-cyclopentoxo-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclobutylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopentylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
15 3-cyclohexylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclohexylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-(1-phenylethyl)sulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-ethylsulfinimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
20 3-ethylsulfonimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfinimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-isopropylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopropylmethoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
25 3-cyclobutoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-cyclopentoxo-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopentylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
30 7-chloro-3-cyclohexylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-cyclohexylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-(1-phenylethyl)sulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-ethylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-chloro-3-ethylsulfinimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

- 7-chloro-3-ethylsulfonimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 7-chloro-3-isopropylsulfonimidoyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 7-chloro-3-isopropylsulfinyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 7-chloro-3-cyclopropoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 5 7-chloro-3-cyclopropylmethoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 7-chloro-3-cyclobutoxy-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 7-chloro-3-cyclopentoxo-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-ethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-propylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 10 3-cyclopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-(1,2-dimethylpropyl)sulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-isobutylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-ethoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-propoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 15 3-isopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-(1,2-dimethylpropoxy)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-isobutoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-isopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-isopropoxy-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 20 3-ethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 7-chloro-3-ethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-ethylsulfanyl-7-methyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-ethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-isopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 25 7-chloro-3-isopropylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-isopropylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 7-chloro-3-cyclopropylmethylsulfanyl-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
 3-cyclopropylmethylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide
 30
10. Compounds according to any one of the preceding claims which acts as openers of the K_{ATP} -regulated potassium channels.
11. A method of preparing a compound of formula I, characterized in

a) reacting a compound of formula II:



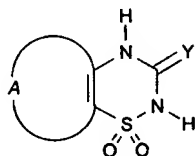
(II)

wherein Y is O or S and A is as defined above with a compound of formula III



in the presence of a base, wherein R^3 is as defined above and X is a leaving group selected from chloro, bromo or iodo to form a compound of the general formula I wherein Z is O or S, or

b) reacting a compound of formula II:



(II)

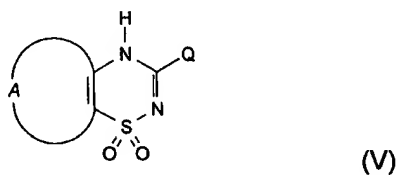
wherein Y is O and A is as defined above with a diazo compound of formula IV



wherein R' and R'' together as two substituents on methyl form a group R'R''CH meeting the criteria defined above for R³, to form a compound of the general formula I wherein Z is O and R³ is R'R''CH, or

5

c) reacting a compound of formula V:



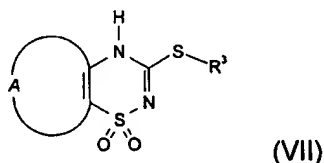
10 wherein Q is a leaving group selected from chloro, bromo, iodo, amino, trimethylamino, imidazol-1-yl, methylsulfanyl, methylsulfinyl or methylsulfonyl with a compound of formula VI:



15

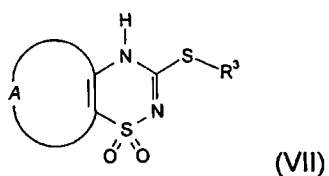
in the presence of a base, wherein R³ is as defined above and Y is O or S to form a compound of the general formula I wherein Z is O or S, or

20 d) reacting a compound of formula VII:



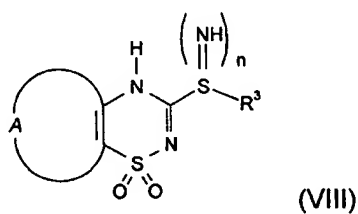
25 wherein A and R³ are as defined above with an oxidizing agent to form a compound of the general formula I wherein Z is S(=O) or S(=O)₂, or

e) reacting a compound of formula VII:



5

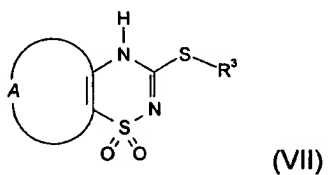
wherein A and R³ are as defined above with an aminating agent to form a compound of the general formula VIII



10

wherein n is 1 or 2, or

f) reacting a compound of formula VII:



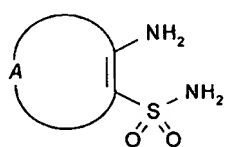
15

wherein A and R³ are as defined above with an aminating agent and subsequently an oxidizing agent, or vice versa, to form a compound of the general formula I wherein Z is S(=O)(=NR), or

20

g) reacting a compound of formula IX

38



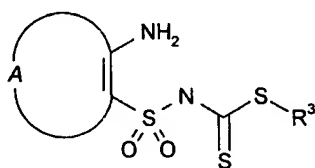
(IX)

- 5 wherein A is as defined above with CS₂ in the presence of a base to give the corresponding sulfonylimino carbodithioate which in turn is treated with an alkylating agent of formula III

R³-X

(III)

- 10 wherein R³ is as defined above and X is a leaving group selected from sulfate, chloro, bromo or iodo to form a compound of formula X



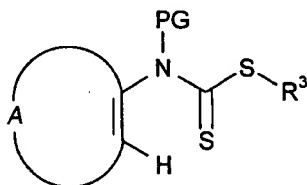
(X)

15

which by ring-closure, e.g. by treatment with phosgene in a solvent, forms a compound of the general formula I, or

h) reacting a compound of formula XI

20



(XI)

- wherein A and R³ are as defined above and PG is a protecting group, selected from substituted benzyl, with chlorosulfonyl isocyanate (Cl-SO₂-NCO) and subsequent ring closure followed by removal of the protecting group to form a compound of formula I.
- 25

12. A pharmaceutical composition comprising a compound according to any of the claim 1 - 9 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or
5 base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

13. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as hyperinsulinaemia and diabetes comprising a compound
10 according to any of the claims 1 - 9 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

14. The pharmaceutical composition according to claim 12 or 13 in the form of an oral dosage unit or parenteral dosage unit.

15. A pharmaceutical composition according to claim 12 or 13 wherein said compound is administered as a dose in a range from about 0.05 to 1000, preferably from about 0.1 to
20 500 and especially in the range from 50 to 200 mg per day.

16. A compound according to any one of the claims 1 - 9 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for
25 therapeutical use.

17. A compound according to any one of the claims 1 - 9 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for
30 therapeutical use in the treatment or prevention of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes.

18. The use of a compound according to any one of the claims 1 - 9 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or

any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form as a medicament.

19. The use of a compound according to any of the claims 1 - 9 for preparing a
5 medicament.

20. The use of a compound according to any one of the claims 1 - 9 or a
pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or
any optical isomer or mixture of optical isomers, including a racemic mixture, or any
10 tautomeric form for the preparation of a medicament for the treatment or prevention of
diseases of the endocrinological system, such as hyperinsulinaemia and diabetes.

21. A method of treating or preventing diseases of the endocrinological system, such as
hyperinsulinaemia and diabetes in a subject in need thereof comprising administering an
15 effective amount of a compound according to any of the claims 1 - 9 to said subject.

22. A process for the manufacture of a medicament, particular to be used in the
treatment or prevention of diseases of the endocrinological system, such as
hyperinsulinaemia and diabetes which process comprising bringing a compound of formula I
20 according to any of the claims 1 - 9 or a pharmaceutically acceptable salt thereof into a
galenic dosage form.

23. Any novel feature or combination of features as described herein.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00559

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 513/04, A61K 31/54 // (C07D 513/04, 285:00, 221:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Tetrahedron, Volume 54, No 44, October 1998, Colin G. Neill et al, "Synthesis of Pyrido-1,2, 4-thiadiazines Related to Antihypertensive 1,2, 4-Benzothiadiazine-1,1-dioxides", page 13645 - page 13654, see page 13647, Scheme 1; page 13651 --	1-23
X	WO 9726264 A1 (NOVO NORDISK A/S), 24 July 1997 (24.07.97), page 17, line 25 - line 34; page 27, line 15 - line 19, the claims --	1-23
X	EP 0618209 A1 (ADIR ET COMPAGNIE), 5 October 1994 (05.10.94), page 25, line 22 - page 26, line 31 --	1-19,21-23

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 March 1999

Date of mailing of the international search report

26-03-1999

Name and mailing address of the ISA/

Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Gerd Strandell

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00559

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 36, No 21, 1993, Bernard Pirotte et al, "3-(Alkylamino)-4H-pyrido 4, 3-e -1,2,4-thiadiazine 1,1-Dioxides as Powerful Inhibitors of Insulin Release from Rat Pancreatic B-Cells: A New Class of Potassium Channel Openers?", page 3211 - page 3213, page 3212, Scheme I --	1-23
X	J. Med. Chem., Volume 39, No 4, 1996, Pascal de Tullio et al, "3- and 4-Substituted 4H-Pyrido 4,3-e -1,2,4-thiadiazine 1,1-Dioxides as Potassium Channel Openers: Synthesis, Pharmacological Evaluation, and Structure-Activity Relationships", page 937 - page 948, page 938, Scheme 3a; page 939, Scheme 4a --	1-23
X	Derwent's abstract, No 10909 C/06, week 8006, ABSTRACT OF SU, 664965 (URAL KIROV POLY), 30 May 1979 (30.05.79) --	1-19, 21-23
X	STN International, File CAPLUS, CAPLUS accession no. 1979:439441, Document no. 91:39441, Kotovskaya, S.K. et al: "Synthesis and properties of pyrido 2,3-e -1,2,4-thiadiazine 1,1-dioxides"; Khim.-Farm. Zh. (1979), 13(4), 54-7 -- -----	1-19, 21-23

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK98/00559

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18, 21
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 18, 21 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/03/99

International application No.
PCT/DK 98/00559

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9726264 A1	24/07/97	AU 1437097 A	11/08/97
		CA 2241565 A	24/07/97
		CZ 9802205 A	16/12/98
		EP 0877748 A	18/11/98
		NO 983285 A	16/09/98
		US 5792764 A	11/08/98

EP 0618209 A1	05/10/94	SE 0618209 T3	
		AT 174920 T	15/01/99
		AU 673893 B	28/11/96
		AU 5904894 A	29/09/94
		CA 2119853 A	27/09/94
		DE 69415373 D	00/00/00
		FR 2703051 A,B	30/09/94
		JP 2513989 B	10/07/96
		JP 7002872 A	06/01/95
		NZ 260186 A	26/07/95
		US 5459138 A	17/10/95
		ZA 9402131 A	05/04/95
